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Antidotes to coumarins, isoniazid, methotrexate and thyroxine, toxins that work via metabolic processes

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Some toxins cause their effects by affecting physiological processes that are fundamental to cell function or cause systemic effects as a result of cellular interaction. This review focuses on four examples, coumarin anticoagulants, isoniazid, methotrexate and thyroxine from the context of management of overdose as seen in acute general hospitals. The current basic clinical pharmacology of the toxin, the clinical features in overdose and evidence base for specific antidotes are discussed. The treatment for this group is based on an understanding of the toxic mechanism, but studies to determine the optimum dose of antidote are still required in all these toxins except thyroxine, where treatment dose is based on symptoms resulting from the overdose.

Introduction

This article will deal with antidotes for a small number of toxins that act to cause their clinical effects on fundamental metabolic processes. Although these toxins act in different ways, they are all uncommon poisonings where there is usually a delay in the toxicity due to the kinetic–dynamic relationship between toxin and metabolic process. In some cases this means the drug is undetectable by the time clinical effects even occur (e.g. thyroxine) or antidote use is difficult to titrate because of this delay (e.g. coumarins and vitamin K). In all cases the acute overdose of these toxins differs from toxicity due to supra-therapeutic or inadvertent iatrogenic toxicity.

Coumarin anticoagulants alter the synthesis of vitamin K dependent clotting factors by directly affecting their synthetic pathway in the liver. The effect of overdose with these agents is therefore an increased risk of bleeding.

The anti-tuberculosis agent isoniazid acts to alter pyridoxine metabolism and this in turn affects the synthesis of GABA, an inhibitory transmitter in the CNS. Acute isoniazid poisoning is consistent with effects of acute pyridoxine deficiency, including convulsions resistant to conventional therapy. Methotrexate is an anti-metabolite that interferes with the actions of folate in cellular synthesis, and in excess this action results in cell death in dividing cells. Thus toxicity particularly affects the bone marrow and gastrointestinal tract. The naturally occurring hormone thyroxine is converted into an active metabolite tri-iodothyronine (T3), which is more potent than the parent hormone. These hormones increase metabolic activity, and the activity of the sympathetic nervous system, causing tachycardia and tremor. These effects may take some days to become fully evident following acute overdose of thyroxine.

Each of the different toxins will now be considered in some detail to emphasise the mechanisms by which the toxins cause their effects and the mode of action of their respective antagonists, and the evidence for their use. The focus will be the management of acute overdose, rather than treating iatrogenic toxicity, such as in the management of warfarin anticoagulation, or intravenous methotrexate use in cancer chemotherapy.

Coumarin anticoagulants

Clinical pharmacology

All coumarins act as antagonists of the synthesis of vitamin K dependent clotting factors II, VII, IX and X. Warfarin

inhibits vitamin K epoxide reductase complex one (VKORC1) and thus prevents reduction of vitamin K to vitamin KH2, a key cofactor in the carboxylation and activation of these clotting factors. The most important coumarin is warfarin, a first generation coumarin, which is a mixture of two isomers, R- and S- forms, of which the S isomer is more potent. The half-life of warfarin varies between 20 and 60 h with a mean of 40 h [1] which can result in prolonged anticoagulation in overdose (Figure 1).

Longer acting coumarin anticoagulants are the second generation 4-hydroxycoumarin derivatives developed in the 1970s because of resistance in rats to warfarin and other first generation 4-hydroxycoumarins [2]. They are sometimes referred to as superwarfarins. The most common member of this group is brodifacoum. Because of their chemical structure they are more potent and have longer half-lives, up to 56 days [3] than warfarin, resulting in an anticoagulation effect lasting months [4].

Warfarin toxicity

The excess effects of warfarin, seen clinically as over-anticoagulation and bleeding, can occur following overdoses of patients receiving warfarin therapeutically, overdoses in patients not prescribed warfarin and an abnormal INR in patients on routine therapy. The approach to managing these different situations is dictated by the necessity of maintaining an anticoagulant effect in patients on warfarin therapeutically.

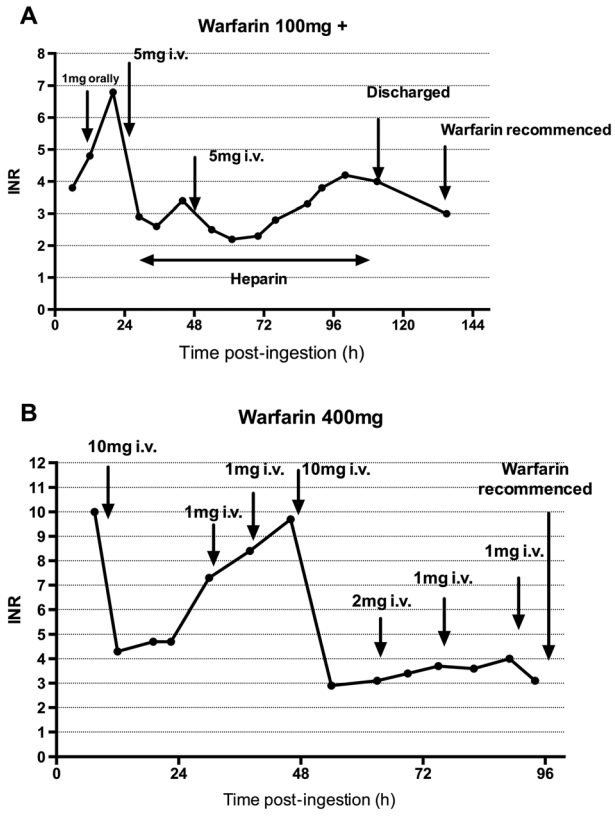

Figure 1

Warfarin overdoses in two patients with mechanical heart valves. A) dose of warfarin in excess of 100 mg B) acute ingestion of 425 mg. Vertical arrows indicate doses of vitamin K and the route (oral or i.v.)

Patients on routine warfarin therapy who have an abnormal INR are discussed elsewhere in guidelines developed by major haematology societies [5–7]. These are in general agreement and recommend, in addition to ceasing warfarin temporarily, using one to two small doses of vitamin K in asymptomatic patients with elevated INRs. In patients who are bleeding they recommend in addition to larger doses of vitamin K (i.e. 5–10 mg), the use of specific clotting factor replacement products and/or fresh frozen plasma.

Warfarin action is measured clinically using the prothrombin time, which is normally reported as the International Normalized Ratio (INR). The laboratory measurement of INR is reasonably accurate across the therapeutic range, but becomes less precise at readings well outside the range. In addition, there is little evidence to help interpret the potential risk of bleeding in acute overdose based on the INR. The closest evidence we have is from patients on warfarin therapeutically suggesting an exponential risk of major bleeding when the INR exceeds 4.5 [8–10].

In acute overdose, the toxic dose is thought to be over 0.5 mg kg^{-1} [11]. The effect of warfarin on INR will be evident by 24 h. However the full effect may not be seen until 48–72 h because of the effect on the vitamin K dependent clotting factors that have longer half-lives e.g. 60 h for prothrombin in comparison with 6 h for factor VII. Similarly the change in INR with the use of vitamin K will be evident within hours but will also take much longer to achieve the full effect. In addition any effect of vitamin K may be short lived and doses need to be repeated due to the long half-life of warfarin in comparison with vitamin K, as well as the higher concentrations of warfarin seen in overdose, in comparison with those in therapeutic excess.

Management

There are no published guidelines on the management of the patient with warfarin overdose although published case reports [11–13] and case series [14] guide us on management principles. Treatment approach depends on the presence or absence of bleeding, or perceived risk of bleeding, based on clinical status, the magnitude of the INR, and the indication, if present, for warfarin, for example atrial fibrillation or mechanical heart valve.

In acute overdose regular repeated INR tests (initially every 4–6 h) are needed to provide a clear idea of the full anticoagulant effect. The patient not normally on warfarin is often treated more aggressively with vitamin K (e.g. 10 mg i.v. or oral) than a patient who requires continued anticoagulant effect for a therapeutic purpose. All the reported cases used i.v. or oral vitamin K

for patients deemed at high risk. The i.v. route carries a small risk of anaphylaxis, [15] and potential problems in re-establishing normal anticoagulant control if larger doses of vitamin K are used. In acute poisoning small doses of regular i.v. vitamin K (1–2 mg every 4–6 h) have been advocated in incremental doses to address both these aspects [12, 16] and to maintain vitamin K levels with higher doses e.g. 5–10 mg sometimes required [11, 13, 14]. There is evidence that i.v. vitamin K may act more rapidly than oral, but by 24 h the magnitude of effect seems similar by the two routes [17, 18]. Figure 1 gives two recent examples of a warfarin overdose in patients with mechanical heart valves managed by one of the authors (CP) demonstrating the large doses of vitamin K required, the variable response to vitamin K, the rebound in INR post-vitamin K and the difficulty of maintaining a safe INR despite regular INR testing and close patient monitoring.

In children, reports of warfarin ingestion are rare. However an estimate of toxic doses of warfarin can be extrapolated from one study in children receiving warfarin therapeutically [19]. A dose of <0.5 mg kg^{-1} results in a prothrombin time of <1.5 times normal and therefore can be considered safe. Doses of 0.5 mg–0.7 mg kg^{-1} result in prothrombin times of 1.5–2.5 times normal and doses >0.7 mg kg^{-1} result in excessive prothrombin times. Vitamin K doses in the range of 0.25 mg kg^{-1} are recommended if required for correction of the coagulopathy (e.g. TOXINZ [www.toxinz.com] accessed July 2015).

The use of factor replacement in acute overdoses is controversial but perhaps should be reserved for patients with active bleeding, which is uncommon in acute overdose [14]. Although guidelines provide suggestions for what type of factor replacement is appropriate in therapeutic over anticoagulation, in acute overdose an empirical approach is reasonable.

Longer acting (superwarfarins) coumarin overdose

Overdose of these agents in adults results in prolonged anticoagulation for several months, with a similar extension in the use of treatment with vitamin K [20, 21]. The INR may take longer to rise and an effect may not be seen until 48 h. Some of these patients present with bleeding, and clotting factor replacement is often required in addition to much larger doses of vitamin K (50–100 mg i.v.), in comparison with warfarin overdose. Reports in overdose [3, 4, 20] suggest a close relationship between the prothrombin time (PT) in seconds and the daily dose of vitamin K required. Once the patient has been stabilized with i.v. vitamin K and clotting factors, we would recommend that 50 mg twice daily vitamin K orally is a starting point for management with up or down titration based on an INR/PT taken prior to the next dose of vitamin K. Compliance with this therapy may be difficult to achieve in some self-harm patients. Use of the actual concentration of the toxin may assist therapy by confirming a concentration unlikely to cause toxicity [20].

In children, large case series of superwarfarin exposures suggest that single one off accidental exposures do not result in toxicity, and that therefore no treatment or follow-up is normally required [22–24]. Rare cases of children presenting with bleeding from ongoing exposure (accidental or deliberate) have been reported [25, 26] and required similar management to adults with superwarfarin toxicity.

A suggested approach to different scenarios is shown in Table 1. Further studies are needed to predict the precise vitamin K dose for a given patient. Advances in pharmacogenomics may assist in vitamin K dose prediction. Overcorrection of INRs will require heparin or low molecular weight heparins as a bridge to re-warfarinization depending on the individual patient scenario.

Isoniazid

Clinical pharmacology

Isoniazid was introduced as a treatment for tuberculosis in the 1950s [27]. It was soon found to cause peripheral neuropathy, which was established in 1954 as being due to a deficiency in pyridoxine (vitamin B6) [28]. Isoniazid is rapidly and completely absorbed with very low protein binding ($<10\%$). Its metabolism is subject to polymorphic acetylation, with fast and slow acetylators having half-lives between 1 and 4 h, respectively [29].

Toxicity

The toxic mechanism of action of isoniazid is through pyridoxine metabolism via a number of mechanisms. In chronic therapy it produces a pyridoxine deficiency by increasing the renal excretion of pyridoxine. In addition it inhibits pyridoxine kinase, the enzyme responsible for the production of pyridoxal phosphate, which is the active form of pyridoxine. Pyridoxal phosphate is a co-factor in the synthesis of gamma aminobutyric acid (GABA) from glutamate by L-glutamic acid decarboxylase [30]. Depletion of GABA, a major inhibitory neurotransmitter of the central nervous system, resulting from an isoniazid-induced pyridoxine deficiency is a major factor in the pathogenesis of isoniazid-induced seizures [30, 31]. In animals a dose-related effect of isoniazid on GABA concentrations in brain has been shown [32]. Studies in animals show a synergy between pyridoxine and diazepam (a GABA-A, benzodiazepine site agonist) in reducing isoniazid induced seizures, but no benefit of phenytoin (a sodium channel antagonist), further supporting a fundamental role of GABA in isoniazid induced seizures [33].

As little as 1.5 g isoniazid have been reported to cause mild toxicity and doses in the range of 6–10 g may result in severe toxicity, with fatalities above 15 g reported, but these were before the advent of modern intensive care

Table 1

Specific management of short acting (warfarin) and long acting (superwarfarins) coumarin overdose

Scenario	Assessment	Therapy	Monitoring
Warfarin acute overdose: patient not on warfarin (adults and children)	In patients ingesting >0.5 mg kg^{-1} perform INR. Effect will be seen by 24 h and be maximal at 48–72 h.	Vitamin K 10–20 mg i.v./orally twice daily (adults) or 0.25 mg kg^{-1} twice daily (children) for a week* Clotting factor replacement plus vitamin K for active bleeding†.	INR every 4–6 h if observing for toxicity. If vitamin K commenced repeat INR to confirm adequate vitamin K dosing. Aim for INR <2‡
Warfarin acute overdose: patient on warfarin therapeutically	In patients ingesting >0.5 mg kg^{-1} perform INR, repeated every 4–6 h until stable.	Smaller doses of i.v. vitamin K if INR above 5 e.g. initial dose of 1 to 2 mg. Higher doses e.g. 5–10 mg if INR >10. Clotti.ng factor replacement plus vitamin K for active bleeding†.	As above Aim for INR <5§ Bridging anticoagulation may be required if INR < recommended for warfarin indication.
Long acting coumarins (superwarfarins): adults	Perform INR, repeated at 4–6 h. Effect will be seen by 48 h. If normal at 48 h, discharge patient otherwise continue to monitor INR for peak effect.	Titrate i.v. vitamin K to effect. Large doses of vitamin K up to 50–100 mg may be required. Clotting factor replacement plus vitamin K for active bleeding.	Monitor INR at least daily while titrating vitamin K. Once stabilized on vitamin K, monitor INR weekly to ensure compliance. Aim for INR <2.‡ Patients will need to be admitted to cease vitamin K to assess if ongoing toxicity.
Long acting coumarins (superwarfarins)Children	No INR monitoring is required for one off exposures. Return if any signs of abnormal bleeding.	As above if toxicity is evident.	As above if toxicity is evident.

*Follow=up INRs to assess vitamin K dosing. †Larger doses of vitamin K will be required. ‡Patients not on warfarin (and patients with superwarfarin ingestion) who have toxicity can be discharged once stabilized on vitamin K and INR <2 §Patients on warfarin therapeutically will need to remain in hospital for vitamin K treatment and to recommence warfarin

units [34]. Clinical features of acute isoniazid overdose include seizures, metabolic acidosis and coma. Since absorption of isoniazid is rapid, clinical features in acute overdose are seen soon after ingestion [31, 35]. It has been suggested that the seizures cause the acidosis [36], although it has been reported in a case with coma treated with mass-equivalent doses of pyridoxine [37].

Evidence for management of toxicity

The specific antidote for CNS features after isoniazid overdose is i.v. pyridoxine, and standard anticonvulsants are generally relatively ineffective due to the lack of intrinsic GABA in the brain, though diazepam is still often used in addition to pyridoxine. There are no controlled studies in humans, and before 1981 different regimens had been used, although there was a suggestion that mass-equivalent doses of pyridoxine might be optimal. This was tested in a case series of five patients whose outcomes were compared with 41 literature cases where other approaches had been used [38]. A key benefit from a mass-equivalent dose was the lack of recurrent seizures, seen in none of these five cases but in 60% of the previous literature cases. A further three patients were subsequently successfully treated using this regimen [39]. There are no studies that look at intermediate doses of pyridoxine, between the lower amounts used prior to the 1980s and the mass-equivalent ones used by Wason and colleagues [38].

Present advice is to use doses up to 5 g pyridoxine, normally given as an equal mass dose to the ingested isoniazid up to this initial maximum, to restore synthesis of GABA. This empirical dosing approach appears to reduce the risk of adverse events with pyridoxine seen after higher dose infusions [40]. Isoniazid is a rare poisoning and lack of rapid availability of i.v. pyridoxine is therefore a potential problem [41, 42]. Oral pyridoxine is a reasonable alternative if i.v. is unavailable. Confusion has been reported as a complication of therapeutic use of isoniazid and was rapidly reversed by i.v. pyridoxine [43, 44]. Hallucinations are also occasionally seen [45].

Haemodialysis will remove isoniazid [46], but is generally not required except perhaps in the most serious cases [36], although in a case of coma the patient did not wake for 3 days despite dialysis [47]. Based on isoniazid's half-life, dialysis should be instituted early if it is going to be effective [46].

In conclusion, in isoniazid overdose acute neurotoxicity responds to pyridoxine, and while the use of a mass-equivalent dose of pyridoxine is effective this may be more than is required for a biologically optimal response (Table 2). Pyridoxine is normally given as the hydrochloride salt, and this statement is based on empirical experience with this salt. The active form of pyridoxine is available in some countries, but it is unclear how the availability of this compound would affect this mass equivalent approach. It could be that lower amounts of this compound might be fully effective, but an uncertainty is the relative CNS availability of the two different formulations.

Table 2
Specific management of isoniazid overdose

Scenario	Assessment	Therapy	Monitoring
Acute isoniazid overdose	Features usually present in 30 min to 2 h. Vomiting, ataxia and decreased conscious level. Observe 6 h.	1. Supportive care with benzodiazepines e.g. midazolam or diazepam for seizures. 2. In patients with symptoms i.v. pyridoxine in a mass equivalent dose to that of isoniazid ingested to a maximum of 5 g. 3. Dialysis for large ingestions >15 g.	Check for acidosis and correct if not resolving. Monitor biochemistry and treat other complications symptomatically.
Chronic isoniazid therapeutic excess	Assess conscious level, history of seizures and metabolic status.	Treat symptomatically. In patients with CNS features use pyridoxine i.v. Effective dose is uncertain, use doses up to 5 g initially.	Monitor clinical status and treat symptomatically.

Methotrexate

Clinical pharmacology

Methotrexate is an antagonist of the enzyme dihydrofolate reductase, blocking the synthesis of tetrahydrofolate and therefore preventing the synthesis of purines and pyrimidines. The major impact of methotrexate is therefore on more rapidly dividing cell systems, typically the gut lining and bone marrow. Important aspects of methotrexate pharmacokinetics are low lipid solubility, saturable oral absorption with renal clearance and negligible liver metabolism. Dosing with methotrexate varies with the indication it is used for. Intrathecal and intravenous doses are used in the management of malignant disease, whereas in the management of rheumatic disease and psoriasis, dosing is often orally once weekly. The patterns of toxicity seen thus differ depending upon the route and quantity of methotrexate administered.

Toxicity

There are four different scenarios of potential methotrexate toxicity – daily oral administration instead of weekly, acute single overdose (deliberate or accidental), toxic concentrations from high dose intravenous cancer therapy (with or without renal impairment) and incorrect doses of intrathecal administration, causing central nervous system toxicity. Because the toxicity of methotrexate is related to area under the curve of the plasma concentration–time curve, toxicity is far more likely with large intravenous doses or inadvertent daily oral dosing, compared with a single acute overdose.

The majority of cases seen by poison centres are due to accidental therapeutic oral excess, often where a once weekly dose is taken daily instead of weekly. In such patients severe toxicity may be seen even after only three daily doses of methotrexate and is characterized by features of bone marrow suppression and sometimes gastrointestinal effects.

A small series of acute single overdoses both in adults and children suggest that they rarely result in toxicity [48]. This is most likely because the gastrointestinal absorption of methotrexate is via a saturable process, which tends to reduce the risk of exposure with acute oral overdose and rapid renal elimination of methotrexate. Acute overdose $<$1000 mg or 5 mg kg^{-1} in children are unlikely to cause any clinical effects [48]. Gastrointestinal effects and bone marrow depression may theoretically occur, but have not been reported.

More severe toxicity is reported with high dose intravenous therapy and dosing errors with intrathecal administration, although uncommon, can cause severe central nervous system toxicity.

Evidence for management of toxicity

There are two potential treatments for methotrexate overdose. The first is the metabolic antagonist folinic acid, which has been used extensively as rescue therapy following intravenous methotrexate for cancer. Recommended doses are outlined in Table 3. The second is the enzyme carboxypeptidase G2 (glucarpidase), which breaks down methotrexate rendering it non-toxic. Glucarpidase is not licensed in all countries (Table 3). Glucarpidase has been used in both intravenous methotrexate toxicity and in intrathecal toxicity. It is expensive and used almost exclusively in the management of patients with cancer who have received inappropriately high doses of methotrexate. It may have a role in the management of cases with renal impairment where it is being shown to reduce methotrexate concentrations significantly [49]. Occasionally excess doses of methotrexate may be given intrathecally, and the treatment here is either to flush the drug from the cerebrospinal fluid or administer intrathecally the carboxypeptidase glucarpidase [50, 51]. The role of folinic acid is less clear, but is often also used in such rare cases.

Most cases seen by poisons centres and in the acute care setting will be due to deliberate overdose or therapeutic error (Table 3). Management of such cases is sometimes problematic because the risk assessment is poorly defined. Toxicity from acute overdose is extremely unlikely, and usually requires no treatment.

Table 3

Specific management of methotrexate overdose

Scenario	Assessment	Therapy	Monitoring
Single oral overdose	Dose ingested <1000 mg or <5 mg kg^{-1} (children) Ensure hydration and normal renal function. No concentration measurements for methotrexate required.	Treatment unlikely to be required unless very high doses ingested. Folinic acid may then be indicated. Decision based on clinical status and if a very high oral ingestion consider obtaining a methotrexate concentration.	Monitor blood count and renal function.
Therapeutic error resulting in excess dosing (weekly dosing taken daily)	Clinical features of methotrexate toxicity (eg blood count, renal function).	Treat with folinic acid if significant features of toxicity. Dose 10 mg m^{-2} i.v./orally every 6 h depending on clinical status.	Monitor blood count and renal function, and other features of toxicity if present.
Single excess i.v. dose in cancer chemotherapy	Usually based on plasma concentration measurement.	Methotrexate >50 μmol l^{-1}; folinic acid 1000 mg m^{-2} i.v. every 6 h. Methotrexate 5–50 μmol l^{-1}; folinic acid 100 mg m^{-2} i.v. every 6 h. Methotrexate 0.5–5 μmol l^{-1}; folinic acid 30 mg m^{-2} i.v./orally every 6 h. Methotrexate less than 0.5 μmol l^{-1}; folinic acid 10 mg m^{-2} orally/i.v. every 6 h. Consider urinary alkalinization, particularly if renal dysfunction, or high flux haemodialysis.	Further methotrexate concentrations, until <0.05 μmol l^{-1}. Full blood count and renal function.
Intrathecal overdose	Based on clinical scenario of excess administration.	Urgent neurosurgical referral for flushing of CSF and potential use of carboxipeptidase G2 (glucopardase).	Severe CNS toxicity may result. In addition systemic features have been reported, and should be monitored for.

For very large overdoses (>1000 mg) folinic acid may be considered, and a full blood count every few days is essential.

In inadvertent daily administration folinic acid should be considered in patients taking methotrexate daily for 3 or more days and daily full blood counts should be done to monitor for bone marrow suppression (Table 3).

Thyroxine

Clinical pharmacology

Thyroxine (levothyroxine, L-thyroxine, T4) is normally converted intracellularly to the active metabolite tri-iodothyronine (T3), which is approximately five times more potent. Thyroid hormones are taken into cells by specific transporter proteins. T3 is thought to be predominantly responsible for the manifestations of excess effects of ingested thyroxine. T3 acts on a nuclear receptor to encode production of proteins including Na/K ATPase and cardiac myosin. Symptom onset is thought to be dependent on the dose of thyroxine administered as well as the conversion rate to T3, and many symptoms appear to relate to sympathetic over activity, likely as a result of excess Na/K ATPase. This means that while symptoms may occur quite early, within 24 h of ingestion, it is more normal for them to appear some days later. Acute measurement of thyroid hormones in blood taken after overdose may be helpful in deciding who to monitor more carefully for symptoms of thyrotoxicosis, but treatment is symptomatic.

Most patients are now prescribed oral thyroxine (T4) although preparations of thyroid extract (e.g. the US Armour Thyroid Tablets) are still available, and these

Table 4

Specific management of thyroid hormone overdose

Scenario	Assessment	Therapy	Monitoring
Single excess oral ingestion	Obtain blood sample for non-urgent measurement of T4, T3 and TSH In those at risk of toxicity check clinical features at 2–3 and 7 days.	Symptomatic therapy with non-selective β-adrenoceptor blocker, e.g. propranolol 40 mg three times daily (caution in asthma). Titrate to response. Treat any other features symptomatically e.g. diazepam for anxiety.	Monitor TFTs if appropriate, and clinical features. For those on therapeutic thyroxine, restart thyroxine when TSH in normal range.
Chronic ingestion/abuse	Obtain blood sample for non-urgent measurement of T4, T3 and TSH. Clinical assessment for features of thyrotoxicosis.	Symptomatic therapy with non-selective β-adrenoceptor blocker, e.g. propranolol 40 mg three times daily. (Caution in asthma). Titrate to response. Remove source of thyroid hormone.	Monitor TFTs if appropriate, and clinical features. For those on therapeutic thyroxine, restart thyroxine when TSH in normal range.

contain both thyroxine and T3. T3 is a hospital only product in the UK, but can be a cause of accidental overdose. Rarely meat contaminated with animal thyroid can enter the food chain and also cause features of hyperthyroidism [52].

Toxicity

The manifestations of thyroxine overdose resemble those of thyrotoxicosis. These include tachycardia, fever, tremor, anxiety, flushing and GI symptoms, such as diarrhoea [53]. In severe cases confusion and seizures may be observed, on occasion several days after the ingestion [54–56].

Ingestion of pure T3 is uncommon, and cases are reported in the literature are rarely T3 alone, but as the active metabolite of thyroxine information on overdose with this agent alone is potentially informative. A 30-year-old woman ingested 1.6 mg of T3, together with brompheniramine and clomipramine [57]. T3 concentration was 80 nmol l^{-1} (0.9–2.8 nmol l^{-1}) at 2 h after ingestion, but apart from mild tachycardia and sweating the patient developed little evidence of significant thyroid effects. Notably TSH was very little suppressed at 7 days.

Factitious thyrotoxicosis can occur from occult ingestion, and both metabolic (TSH and T4 suppression) and physical effects with tachycardia, anxiety and GI features may be seen [58]. Today the greatest risk in the USA appears to come from unlicensed dietary pills which contain T3 [59].

Evidence for management of toxicity

Although thyroid hormone excess is potentially a severe event, in most cases effects are mild. There are little data on the optimum management of thyroid hormone excess. The evidence base is case reports, many in children who develop few features of toxicity [60–62]. Based on these reports, doses of <2 mg or 0.13 mg kg^{-1} in children are unlikely to result in adverse effects [63]. In adults there are fewer reports to guide us but >5 mg is required to produce symptoms of thyrotoxicosis [53, 64, 65]. In those taking potentially toxic doses, monitoring is required, which may be as an outpatient in those who are asymptomatic. A measurement of thyroid hormone levels at presentation may guide need for future monitoring intensity, but is not normally required as an urgent result.

Management of symptoms is the same as for thyrotoxicosis, with non-selective β-adrenoceptor antagonists such as propranolol [56, 66–68] being the mainstay of management (Table 4). Doses of propranolol should be titrated to clinical response, and in patients with asthma, more careful monitoring is required. Activated charcoal and cholestyramine are potential therapies to reduce thyroxine absorption, but there are no controlled data in overdose. Other specific therapies such as extracorporeal removal may be required rarely for very large overdoses with severe toxicity [69].

Competing Interests

There are no competing interests to declare.

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